CXCL14-CXCR4 Axis Drives Treg-Mediated Immunosuppression and Confers Resistance to PD-1 Blockade in Lung Adenocarcinoma

Zhang Yang[1,2,3], Guoliang Liao[1,2,3], Jun Wu[4], Xun Jiang[1,2,3], Jiekun Qian[1,2,3], Qinzhao Huang[1], Xian Gong[1],Yiming Chen[1],Bin Zheng[1,2,3], Chun Chen[1,2,3]

[1]Fujian Medical University Union Hospital, Fuzhou/CN, [2]Clinical Research Center for Thoracic Tumors of Fujian Province, Fuzhou/CN, [3]National Key Clinical Specialty of Thoracic Surgery, Fuzhou/CN,[4]School of Pharmaceutical Sciences,Xiamen University

Correspondence: *Chun Chen (chenchun0209@163.com)*

IASLC 2026 World Conference on Lung Cancer
SEPTEMBER 12 – 15, 2026
SEOUL, REPUBLIC OF KOREA

INTRODUCTION

Immunosuppressive tumor microenvironment (TME) is a major determinant of resistance to immunotherapy in lung adenocarcinoma (LUAD). Although CXCL14 has been implicated in tumor biology, its role in shaping the immune landscape and regulating T cell function remains poorly defined.

METHODS

Integrated bioinformatics analyses of TCGA-LUAD datasets were performed to evaluate the association between CXCL14 expression and immune infiltration. Functional assays, including naïve CD4⁺ T cell differentiation, CRISPR/Cas9-mediated CXCL14 knockout, and in vivo tumor models, were conducted to delineate its immunomodulatory role. Molecular interaction between CXCL14 and CXCR4 was assessed by GST pull-down and docking analyses. Pharmacological inhibition and combinatorial immunotherapy were evaluated in vivo.

DISCUSSION AND CONCLUSION

CXCL14 binds to its receptor CXCR4 and effectively facilitates the differentiation of Treg. This biological event further remodels the TME toward an immunosuppressive phenotype. Accumulating evidence has demonstrated that immunosuppressive TME is one of the dominant contributors to PD- 1 blockade resistance. Therefore, therapeutic targeting of the CXCL14- CXCR4 axis, when combined with PD- 1 immune checkpoint inhibitors, could serve as a promising combinatorial therapeutic strategy. This dual- target regimen is expected to reverse immunotherapy resistance and improve clinical therapeutic efficacy for patients with LUAD.

REFERENCES & ACKNOWLEDGEMENTS

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We thank all patients for participating in this study. We appreciate the technical support from Fujian Medical University Union Hospital and Clinical Research Center for Thoracic Tumors of Fujian Province. We also thank our lab members for helpful discussions.

RESULTS

Elevated CXCL14 expression was significantly associated with increased Treg infiltration and immunosuppressive signatures, including PD-1, CTLA-4, IL-10, and TGF-β. Mechanistically, CXCL14 directly interacted with CXCR4 and promoted differentiation of naïve CD4⁺ T cells into Tregs, without directly affecting CD8⁺ T cell exhaustion. CXCL14 depletion suppressed tumor growth and reshaped the TME by reducing Treg infiltration and enhancing CD8⁺ T cell activity. CXCR4 blockade abrogated CXCL14-induced Treg differentiation. Notably, CXCR4 inhibition synergized with PD-1 blockade, and this effect was further potentiated by CXCL14 depletion.

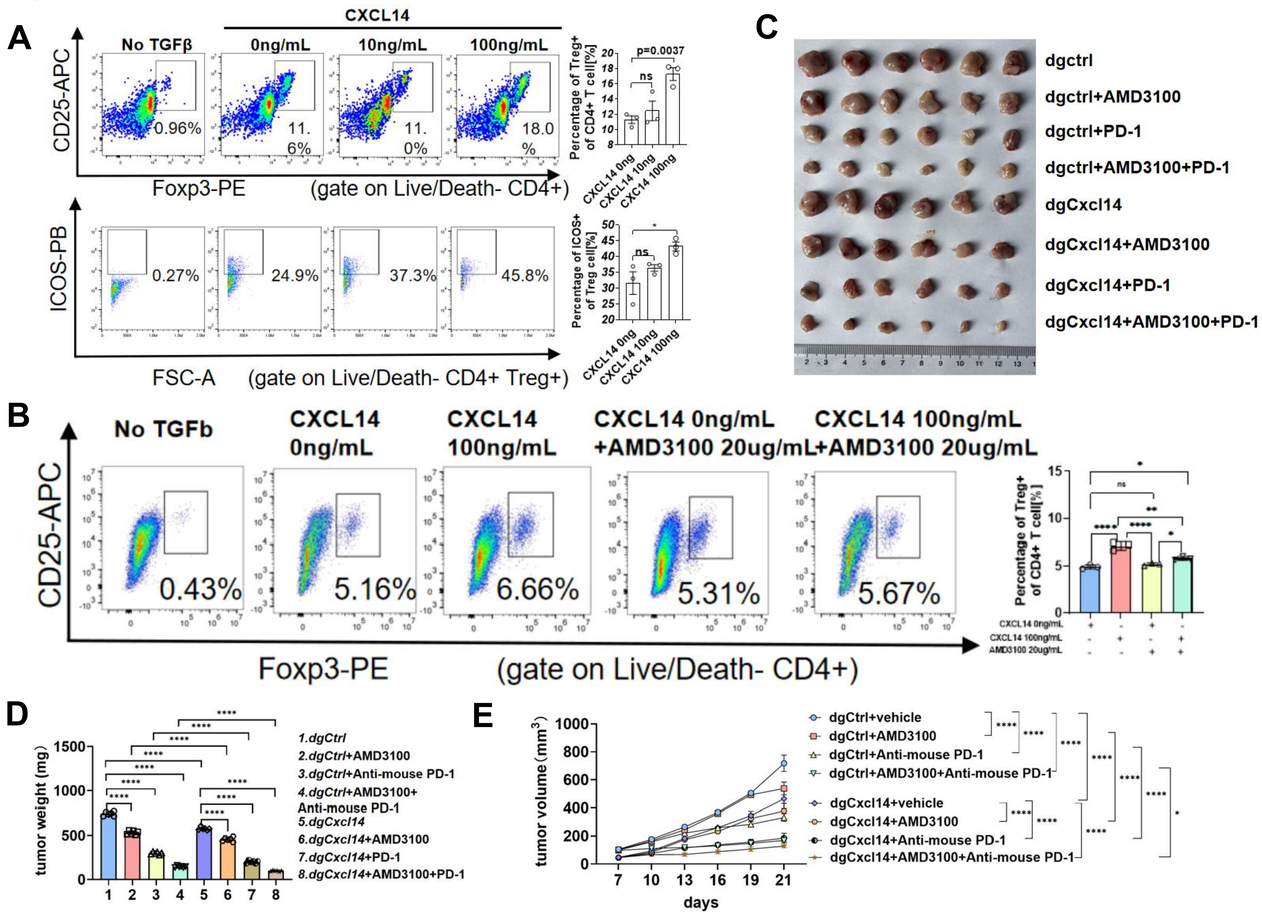


Figure 1. CXCL14-CXCR4 axis induces Treg differentiation and enhances the therapeutic effect of PD-1 blockade in LUAD.
(A) Flow cytometric plots of CD25⁺Foxp3⁺ Tregs induced by increasing CXCL14 concentrations. ICOS expression indicates Treg activation.
(B) Flow analysis showing AMD3100 reverses CXCL14-mediated Treg differentiation.(C) Images of isolated tumors from xenograft models.
(D) Tumor weight. (E) Tumor growth curves.